REMARKS

Reconsideration of the rejections set forth in the Office action mailed June 29, 2004 is respectfully requested, for the reasons discussed below. Claims 1-11, 15-17 and 19-27 are currently pending.

I. Amendments

Claim 1 has been amended to replace the language "a population of duplexes comprising different oligomeric analyte molecules" with "a population of duplexes, each comprising one of a population of different oligomeric analyte molecules hybridized with a specific probe molecule", to clarify the composition of the duplexes. The language "are able to hybridize..." has been deleted from the claim, since the foregoing language already recites that the analyte molecules are "hybridized with" the probe.

Dependent claim 6 has been amended to recite that "the probe has a length which is equal to, or up to 25% greater than, the length of the selected sequence". See, for example, original claim 6 and the specification at page 9, lines 8-12.

Dependent claim 16 has been amended to recite a "charge bearing separation medium", in accordance with the language of parent claim 1.

No new matter is added by any of the amendments.

II. The Invention

A. Benefits of the Invention

As discussed in the Background of the specification, highly charged oligomers, such as nucleic acids, are commonly separated using charge-based separation methods, such as ion exchange chromatography or electrophoresis. However, such methods have been less useful for separation of substantially uncharged oligomers. Conventional ion exchange separation of oligonucleotide analogs having uncharged linkages generally requires ionization of the base moieties, by carrying out the separation at very high pH (>11), at which G and T bases ionize, or at very low pH (<3), at which C and A bases ionize. However, some types of linkages are unstable at these extreme pH levels. (See applicants' specification, page 1, lines 18-22.)

The present method, which can be carried out at neutral or near-neutral pH, employs a specific fully charged probe molecule, as recited in claim 1, which hybridizes with some or all of

the analyte molecules. It is the discovery of the applicants that these duplexes of the different, substantially uncharged analyte molecules with the fully charged probe molecule can be separated in a charge-bearing medium, even when all the duplexes are identically charged (as is the case with fully uncharged, or identically charged, analyte molecules). This is shown by the working examples, which are briefly described below.

It is believed that separation occurs on the basis of differing amounts of unconstrained single stranded probe molecule in the different duplexes. See the discussion at page 9 of the specification, with reference to Figs. 3-4.

B. Working Examples

To illustrate the method, Example 1 shows separation of duplexes of a specific probe DNA with several uncharged oligomers which vary in length from 13 to 20 subunits (Example 1, page 15; Figs. 5A-B).

Example 2 shows separation of duplexes of a specific probe DNA with several same-length uncharged oligomers, where the oligomers differ in sequence only by deletion of one nucleotide subunit at various positions (Example 2, page 16; Figs. 6-8).

III. Rejections under 35 U.S.C. §112, Second Paragraph

The pending claims were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner's points are addressed as follows.

Claim 1 has been amended to replace the language "a population of duplexes comprising different oligomeric analyte molecules" with "a population of duplexes, each comprising one of a population of different oligomeric analyte molecules hybridized with a specific probe molecule", to clarify the composition of the duplexes.

The Examiner stated that claim 6 recited "two different ranges" for the length of a probe, namely "no more than" and "25% greater". The applicants believe this is a misinterpretation, since "no more than" is intended to modify "25%". That is, the probe of this claim could be the same length, 5% longer, 10% longer, or 15% longer than the selected sequence, but it cannot be 50% longer, since this is more than 25%. The Examiner's assumed interpretation of "equal to or no more than 25% of the selected sequence" is not the intended meaning of the claim.

In an attempt to clarify the intended meaning, claim 6 has been amended to recite that "the

probe has a length which is equal to, or up to 25% greater than, the length of the selected sequence".

Claim 16 has been amended to recite a "charge bearing separation medium", in accordance with the language of parent claim 1.

In view of the foregoing, the applicants submit that the now pending claims comply with the requirements of 35 U.S.C. §112, second paragraph.

IV. Rejections under 35 U.S.C. §102(b)

Claims 1-11, 16-17, 19-20, and 23-27 were rejected under 35 U.S.C. §102(b) as being anticipated by Cummins *et al.*, U.S. Patent No. 5,874,213. This rejection is respectfully traversed for the following reasons.

A. The Invention

The applicant's invention, as embodied in independent claim 1, and as discussed above in Section I, provides a method of separating a population of duplexes, each comprising one of a population of different oligomeric analyte molecules, which are substantially uncharged, hybridized with a specific probe molecule, which is fully charged.

Accordingly, each duplex comprises one fully charged probe strand, which is the same in each duplex, and one substantially uncharged analyte strand, which varies.

The method comprises the steps of:

(a) applying the different analyte molecules (substantially uncharged) and the specific probe molecule (fully charged) to a charge-bearing separation medium, under conditions such that the probe forms stable duplexes with a plurality of or all of the analyte molecules,

thereby forming a mixture of species selected from probe-analyte duplexes, single stranded analyte, single stranded probe, and combinations thereof; and

(b) separating the duplexes from each other and from single stranded species within the medium.

B. The Cited Reference

Cummins *et al.* does not disclose step (a) of the applicants' claimed method, namely: "applying to a charge-bearing separation medium a mixture of (i) the different analyte molecules and (ii) the specific probe molecule", wherein the "analyte molecules are composed of linked

subunits of which at least 90% are uncharged", and the "specific probe molecule is a nucleic acid or fully charged nucleic acid analog".

Moreover, the applicants' claims require, in step (b), "separating the duplexes from each other". The only disclosure in Cummins of separation of different duplexes from each other is in Examples 3, 6, and 7 (at column 14, lines 63-67; column 15, lines 39-41; and column 15, lines 48-49, respectively). However, in these procedures, the different duplexes are duplexes of different-length DNAs (which are fully charged) with a single PNA (which is substantially uncharged, having a single lysine residue). Accordingly, these procedures employ a plurality of different, charged "analyte" molecules (e.g. a nucleic acid mixture) and a single, uncharged (or substantially uncharged) "probe" molecule (PNA). This is the opposite of what is recited in the applicants' claim 1; i.e., "wherein said *analyte molecules* are composed of linked subunits of which at least 90% are *uncharged*, and said *specific probe molecule* is a nucleic acid or *fully charged* nucleic acid analog".

In view of the above, the disclosure of the reference does not show the elements of independent claim 1. Accordingly, the applicants request that the rejection under 35 U.S.C. §102(b) be withdrawn.

V. Rejections under 35 U.S.C. §103(a)

Claim 15, which recites an ion exchange separation medium, was rejected under 35 U.S.C. §103(a) as being obvious over Cummins *et al.*, U.S. Patent No. 5,874,213, discussed above, in view of Ness *et al.*, U.S. Patent No. 6,613,508, which discloses ion exchange chromatography as one method of size-based separation of nucleic acids from other molecules (column 4, lines 10-15 and 21).

Claims 21-22, which recite morpholino oligomers, were rejected under 35 U.S.C. §103(a) as being obvious over Cummins *et al.*, U.S. Patent No. 5,874,213, discussed above, in view of Valdivia et al. (WO 96/36734), which notes that PNA and morpholino compounds have certain advantages over nucleic acid probes.

These rejections are respectfully traversed for the following reasons. In brief, the primary reference, Cummins *et al.*, does not teach or suggest the invention of independent claim 1, as discussed below, and the secondary references add nothing pertinent to the invention of independent claim 1.

As discussed above in Section IV, Cummins does not teach a method in which probe/analyte duplexes are separated from each other, where the method employs a "specific probe molecule" which is "a nucleic acid or fully charged nucleic acid analog". As stated above, the "specific probe molecule" in the procedures described in Cummins is uncharged, or substantially uncharged (a PNA), and the "different oligomeric analyte molecules" are fully charged (nucleic acids), which is the opposite of what is recited in applicants' claim 1.

Nor does Cummins provide any motivation, or expectation of success, for carrying out the applicants' method. Cummins *et al.* teaches that it is possible to separate, in a charge-bearing separation medium, duplexes of different-length charged nucleic acids each hybridized with the same uncharged probe molecule. In this case, the duplexes are differently charged, deriving their different charges from the analyte (nucleic acid) molecules. For example, in Example 3, the three duplexes have net charges of -17, -18 and -19 (18-, 19-, and 20-mers of DNA each hybridized with a lysine-terminated PNA).

One skilled in the art armed with this knowledge would not, however, be motivated to attempt to separate, in a charge-bearing separation medium, duplexes of different-length uncharged oligomers each hybridized with the same charged probe molecule. In this case, the resulting duplexes are identically charged, because they derive their charge from the probe molecule, which is the same for each duplex. Cummins' description of separation of differently charged duplexes in a charge-bearing medium provides no expectation of success for separation of identically charged duplexes in such a medium.

The same argument would apply if the "substantially uncharged" analyte molecules in applicants' method bore some charge (having no more than 10% charged subunits, as provided by claim 1) and were identically charged. If identically charged, their duplexes with the same charged probe would also be identically charged. Again, Cummins' description of separation of differently charged duplexes in a charge-bearing medium provides no expectation of success for separation of identically charged duplexes in such a medium.

If the "substantially uncharged" analyte molecules were differently charged (having no more than 10% charged subunits, as provided by claim 1), one skilled in the art would not be motivated, without having read the applicants' disclosure, to hybridize such molecules with the same fully charged probe molecule. The difference between the charge/mass ratios of the analyte molecules, in this case, would be greater without such hybridization. Therefore, to one

without knowledge of the applicants' disclosure, such hybridization would be expected to make separation in a charge-bearing medium more difficult.

In view of the above, the disclosure of Cummins et al. does not teach the claimed method, and it provide no motivation or expectation of success for carrying out the claimed method.

The secondary references are cited for their brief discussions of morpholino oligomers and ion exchange chromatography, respectively, and add nothing to the teachings of Cummins et al. that is pertinent to independent claim 1. Accordingly, the references in combination do not teach or suggest the invention of claim 1, or any of its dependent claims, which include all of its limitations.

In view of the foregoing, the applicants respectfully request the Examiner to withdraw the rejections under 35 U.S.C. §103(a).

VI. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4403.

Respectfully submitted,

Date: Sep. 29, 2004

LeeAnn Gorthey
Registration No. 37,337

Correspondence Address:
PAYOR NUMBER 22918
PHONE: (650) 838-4403
Fax: (650) 838-4350